Jaworski Deposit Acct. No. 55-1212/MYOG:004USDI/SLH. Please amend the application as follows.

AMENDMENT

Listing of Claims

The following listing of claim replaces all previous listings or versions thereof:

23. (Presently amended) A method of treating myocardial failure in a human comprising administering an effective amount of a transgene encoding for α-MHC, wherein ~~said treatment~~ expression of α-MHC provides improvement in left ventricular ejection fraction.

REMARKS

I. Status of the Claims

Claims 1-22 have been canceled, and claim 23 is pending and stands rejected under 35 U.S.C. §112, first paragraph and §112 second paragraph. The specific grounds of rejection, and applicants' responses thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, Second Paragraph

According to the examiner, claim 23 is incomplete in reciting treatment without transgene expression. An amendment has been offered

III. Rejection Under 35 U.S.C. §112, First Paragraph

Claim 23 stands rejected as lacking an enabling disclosure in the specification. According to the examiner, the specification is defective in (a) failing to provide an adequate basis for predicting that an increase in α-MHC transcripts would benefit subjects having myocardial failure, (b) failing to provide correlation of α-MHC transgene expression *in vivo* with therapeutic benefit, and (c) failing to teach or provide guidance with respect to specific levels of α-MHC that would be therapeutic. Applicants provided an extensive response to which the examiner has, for the most part, simply "reiterated" the PTO's previous position. Thus, once again, applicants traverse.

First, applicants again submit that the examiner is incorrect in arguing that there is insufficient evidence that the increase in α-MHC transcripts seen in patients being successfully treated leads to patient benefit. When a messenger RNA level increases, it is common sense that a commensurate increase in protein levels will follow. Of course, this is not always the case, but it is a rare occurrence when protein and message levels do not correlate. Thus, the burden should be on ***the examiner*** to explain why the demonstrated increase in message would not be viewed as predictive of therapeutic efficacy for α-MHC gene therapy, and thus supportive of enablement.

Moreover, applicants have supplemented the evidentiary record with a recent publication and a declaration on this very point.[1] The relied upon study examined MHC expression as a function of improved disease-state phenotype. This study showed a direct correlation between α- and β-MHC levels and a diseased heart state. Importantly, the age variation in the study subjects was minimal: 54.1 ± 10.5 years for tests and 49.1 ± 4.6 years for controls. Thus, the

[1] It is noteworthy that the §112 rejection in the companion '733 application was withdrawn in the face of this very evidence.

study was able to isolate the disease state as a variable and eliminate age as a complicating factor. The results, as attested to in the declaration, provide clear evidence that there is a direct, predictable and statistically relevant correlation between levels of α- and β-MHC and myocardial failure. Thus, absent compelling reason to doubt that the same benefit would be not achieved with gene therapy, enablement should be conceded.

Additionally, the examiner is referred to Jones *et al.*, *J. Clin. Invest.*, 98:1905-1917 (1996), which discusses the ablation of the α-MHC gene and the relationship between α-MHC protein and mRNA levels of α-MHC and LVEF, the measure of heart function applicants use as the standard for improvement in the currently prosecuted claim. Jones found that ablation of both α-MHC alleles led to gross heart defects that were partially rescued by the heterozygous form. This paper further showed that "mammalian left ventricular function can be severely compromised by a gene dosage effect involving" α-MHC, direct support of the notion that increasing the levels of α-MHC (whether exogenously or endogenously) would be beneficial to LVEF. While this paper does not prove that exogenous addition of α-MHC can lead to increased LVEF, it strongly supports the inventor's paradigm, and as a result, coupled with later references regarding gene therapy in the heart, should be seen as sufficient to overcome the examiner's rejection regarding α-MHC.

Second, the examiner questioned what increase in α-MHC is needed to increase left ventricular ejection fraction, and thereby achieve therapy. The above referenced study used β-adrenergic blocking agents to improve the systolic function of subjects who exhibited the idiopathic dilated cardiomyopathy phenotype. The study measured expression levels of several genes and found a direct correlation with improvement in left ventricular ejection fraction and levels of α- and β-MHC. Specifically, as LVEF improved following treatment with β-adrenergic

blocking agents, mRNA levels of α-MHC increased and mRNA levels of β-MHC levels decreased.

In a puzzling comment, the examiner states that "the Examiner's argument is not directed to the correlation of endogenous α-MHC expression with correlation to a disease phenotype." Apparently the examiner misapprehends applicants' previous statements. Applicants' point was that when one has (a) a baseline for normal α-MHC levels; (b) a disease state measure of α-MHC levels; and (c) monitored course of treatment levels for α-MHC, there is absolutely no basis for believing that one of skill in the art could not predict, with a reasonable expectation of success, what *in vivo* levels would be therapeutic. Thus, it is quite misleading and disingenouous to argue that "Applicant fails to show what levels of an α-MHC transgene expression are required to alleviate myocardial failure …," when such information is easily extracted from the information provided and the general knowledge in the field.

In conjunction with information provided in the application and the study described above, there is more than sufficient information on the baselines for normal and abnormal MHC expression. Moreover, the ability to track the elevation of α-MHC levels during the course of treatment provides a "real time" assessment of α-MHC levels as cardiac output improved. Thus, one can very readily determine at what point therapeutic efficacy is achieved. It also is not relevant that "complete amelioration" would be encompassed by therapy. The question is whether "therapy" is supported, and the numerous embodiments short of "complete amelioration" would be sufficient for this.

Moreover, the examiner's comment that "Applicant has not provided guidance or evidence to ***show*** a correlation to therapeutic levels of expression of α-MHC transgene expression in an *in vivo* setting in a subject suffering from myocardial failure" shows that the

examiner is effectively requiring clinical data. As the PTO has been repeatedly admonished by the CCPA and the Federal Circuit, it is ***not*** the FDA. It is the FDA's province to approve therapeutic regimens. It is the PTO's responsibility to determine whether a therapeutic method can be performed by one of skill in the art with a reasonable expectation of success. Here, there is overwhelming evidence that a decrease in α-MHC levels results in cardiac failure and, in the absence of some reason to expect that restoring these levels would not be therapeutic, enablement must be presumed.

Thus, ultimately, the rejection really appears to boil down to an argument over whether or not gene therapy for cardiac tissue is possible. Previously, applicants have provided a number of publications, far more relevant than those cited by the examiner, reporting on the successful transfer of genes into cardiac tissue. Alexander *et al.*, *Clin. Exp. Pharmacol. Physiol.*, 26:661-668 (1999) reported gene transfer into myocardium through direct injection of plasmid DNA and viral transfer. Chien *et al.*, WO/2000/15821 describe the use of recombinant adenovirus-mediated expression of transgenes in both neonatal and mature cardiac tissues. Other papers reporting cardiac transgene expression included Davidson *et al.*, *Circulation* 104:131 (2001), Pachucki *et al.*, *Endocrinology* 142:13 (2001), Shinmura *et al.*, *Japan Heart J.* 41:633 (2000), Silva *et al.*, *FASEB* 14:1858 (2000), Lenhart *et al.*, *Am. J. Physiol. Heart Circ. Physiol.* 279:H986 (2000), Lazarous *et al.*, *Cardiovasc. Res.* 44:294 (1999), and Wickenden *et al.*, *Circ. Res.* 85:1067 (1999). Interestingly, other than to "reiterate" the previous argument, the examiner has failed to even mention this submission.

Despite the examiner's failure to address these previous citations, applicants now provide yet additional references that undercut the examiner's position on enablement. Fromes *et al*, *Gene* Therapy, 12:683-688 (1999) describes the successful delivery of a gene to the myocardium

by intraperitoneal injection. This paper starts by stating that "gene therapy is a potential new strategy for cardiovascular diseases" and goes on to state that "several studies have demonstrated the feasibility of gene transfer into the heart muscle." In addition to this reference, a number of previous references demonstrated the potential of direct injection of genes into the myocardium (*see* Lin *et al*, *Circulation*, 82:2217-2221 (1990); Stratford-Perricaudet *et al.*, *J. Clin. Invest.*, 90:626-630 (1992); Von Harsdorf *et al.*, *Circ. Res.*, 72:688-695 (1993); French *et al.*, *Circ. Res.*, 72:688-695 (1993); Lee *et al.*, *J. Thorac. Cardiovasc. Surg.*, 90:2414-2424 (1994); Coffin *et al.*, *Gene Therapy,* 3:560-566 (1996); and Kypson *et al.*, *J. Thorac. Surg.*, 115:623-630 (1998)). Nonetheless, Fromes constitutes an advance over these reports in developing a technique for "local delivery of the therapeutic gene into the pericardium," demonstrating the successful delivery of a gene to the heart. Fromes' results proved that "intra-pericardial injection ... leads to an efficient and safe strategy to deliver a transgene to the heart." The successful approach taken by Fromes came on the heels of another successful application of cardiovascular gene therapy by Hajjar *et al*, *Proc. Natl. Acad. Sci.*, 95:5251-5256 (1998). Hajjar used a catheter-based technique to successfully alter cardiac function in rat hearts. This study was seen as opening the prospect "of using somatic gene transfer to modulate overall cardiac function *in vivo*."

The success seen by Fromes and Hajjar has been built on by later researchers that validates the feasibility and effectiveness of cardiovascular gene therapy. Schroder *et al.*, *Transplantation*, 70:191-198 (2000) showed that addition of anti-CD4 monoclonal antibodies improved gene transfer into rat cardiac grafts. O'Donnell *et al.*, *Circ. Res.*, 88:415-421 (2001) showed that sarcoplasmic reticulum (SR) ATPase (SERCA), could be expressed in cardiac myocytes. del Monte *et al.*, *Circulation*, 104:1424-1429 (2001) also showed effective transfer of

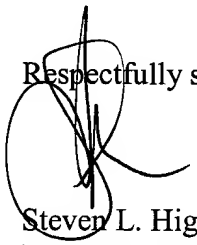
and expression of SERCA2a into a rat heart through adenoviral gene transfer. Li *et al.*, *Gene. Ther.*, 21:1807-1813 (2003) showed that an adenoviral associated vector (AAV) could be successfully used to transfer a reporter gene and a therapeutic gene into the heart of a hamster. Lastly, applicants point to Yue *et al.*, *Circulation* (2003), who went yet a step further and actually treated a cardiovascular disease using an AAV vector to deliver a therapeutic gene to the heart of a diseased mouse. Yue not only delivered the gene but was able to see improvement of cardiovascular function and further saw improvement in disease state.

In short, applicants submit that the present record provides adequate evidence of the value of α-MHC therapy. In addition, the use of gene therapy in cardiac tissue is not so far beyond the realm of possibility that it is non-enabled. Reconsideration and withdrawal is respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Ton have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



September 22, 2003
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